Novel Signs and their Clinical Utility in diagnosing Complex Regional Pain Syndrome (CRPS) - A Prospective Observational Cohort Study

Abstract

Objectives: Delays in diagnosis occur with Complex Regional Pain Syndrome (CRPS). We define and prospectively demonstrate that novel bedside tests measuring body perception disruption can identify patients with CRPS post-fracture.

Methods: The objectives of our study were to define and validate four bedside tests; to identify the prevalence of positive tests in patients with CRPS and other chronic pain conditions and to assess the clinical utility (Sensitivity; Specificity; Positive Predictive value; Negative Predictive Value) for identifying CRPS within a Fracture cohort. **This was a single UK teaching hospital prospective cohort study with** 313 recruits from healthy volunteers and patients with chronic pain conditions.

Four novel tests were Finger Perception (FP), Hand Laterality identification (HL), Astereognosis (AS) and Body Scheme (BS) report. Five questionnaires (Brief Pain Inventory; Upper Extremity Functional Index; Lower Extremity Functional Index; Neglect-like Symptom Questionnaire; Hospital Anxiety and Depression Score) **assessed the multidimensional pain experience.**

Results: FP & BS were the best performing tests. Prospective monitoring of fracture patients showed that out of 7 fracture patients (total n=47) who had both finger misperception and abnormal body scheme report at initial testing, 3 developed persistent pain with 1 having a formal diagnosis of CRPS.

Discussion: Novel signs are reliable, easy to perform and present in chronic pain patients. FP and BS have significant clinical utility in predicting persistent pain in a fracture group thereby allowing targeted early intervention.

Key words: CRPS, Novel Signs, Clinical Utility

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Introduction

Complex Regional Pain Syndrome (CRPS) is a chronic, debilitating pain condition of unknown aetiology that usually arises after trauma to a limb (1). It occurs at an incidence of about 26:100,000, including about 4% post-wrist fracture (2). Every year, about 80,000 Americans are diagnosed with CRPS, equating to an annual lost income in the USA exceeding US$1billion (3,4). Guidelines recommend prompt diagnosis and early treatment to avoid secondary physical problems and the psychological consequences of undiagnosed chronic pain (5) yet patients in the UK with chronic CRPS have had an average diagnostic delay of 6 months (6). The diagnosis of CRPS is clinical and based upon the presence of dis-proportionate pain associated with vasomotor, sudomotor, trophic and motor changes (1). Investigations such as thermography, triple phase bone scan and contrast-magnetic resonance imaging may aid the diagnosis, but have low positive and negative predictive values (7).

Novel clinical signs such as abnormal finger perception (FP), hand laterality identification (HL), astereognosis (AS) and body scheme report (BS) have been reported in patients with CRPS (2,8–12).

Finger perception is defined as the ability to identify fingers correctly with eyes closed when tactile stimuli is applied to the fingers. In a study of 73 CRPS patients Forderruether and colleagues reported that this was impaired in the affected hand compared with those of the contralateral hand in 37 (48%) patients (9).

Hand laterality identification is a motor imagery (mental rehearsal without action) task of recognising the laterality of pictured image of a hand as either left or right.

This requires the mental rotation of the image of one's own hand to match that of the picture. This neurocognitive ability is reported to be impaired in chronic pain conditions including CRPS. For example, in a study of 18 CRPS patients and age matched controls (10), CRPS patients had delayed hand laterality recognition on the affected side which was related to symptom duration and to the pain that would be evoked by executing the movement.

Astereognosis is defined as the inability to identify an object by touch only without visual input despite having intact cutaneous sensation. Classically, this is reported in patients who have had stroke mainly affecting the parietal lobe. This has been reported in some patients with CRPS. For example, Cohen and colleagues (13) reported that in a study of 22 CRPS patients, 14 (64%) had astereognosis.

Body scheme is the dynamic real time representation of one's own body in space. This is generated by the proprioceptive, somatosensory, vestibular and other sensory inputs. This representation is also integrated with motor systems for control of action and normally this integration is automatic and seamless. Abnormal body scheme is reported in CRPS patients and has been proposed as a contributor to pain in this condition. For example, Lewis and colleagues (14) undertook a qualitative study using semi-structured interviews of 27 patients with CRPS and reported that patients revealed bizarre perceptions of affected body parts and that some patients expressed a desire to amputate the affected part despite the prospect of further pain and functional loss.

Neurocognitive dysfunctions thought to be similar to the post-stroke neurological neglect have been reported in CRPS and the term 'neglect-like' or 'depersonalisation' has been used to describe them(15). For example, some CRPS patients perceive their own affected limb to be 'foreign' and not belonging to them

and this was dubbed ‘cognitive neglect’. Similarly, some CRPS patients may need to focus mental and visual attention in order to move their affected limb and this was referred to as ‘motor neglect’.

The novel signs described above represent neurocognitive disturbances of body perception possibly related to somatosensory and motor cortical reorganisation (16). Although the precise pathophysiological basis of these signs remains elusive, they may have diagnostic utility in CRPS. The aims of this prospective observational cohort study were to validate these novel signs as simple bedside tests; assess their prevalence in chronic pain conditions; and to prospectively assess their clinical utility in identifying CRPS in a Fracture cohort.

Methods

Study Population

We recruited patients who were more than 16 years old and able to give informed written consent from the following groups: Chronic upper and/or lower limb CRPS (International Association for the Study of Pain Budapest research criteria (1)); Rheumatoid Arthritis - RA (American Rheumatology Association’s classification criteria (17)); Fibromyalgia Syndrome- FMS (American College of Rheumatology 1990 classification criteria (18)); Chronic Low Back Pain -LBP (European Commission Research Directorate Guidelines (19)) and Upper or lower limb Fracture requiring plaster casting less than two weeks after fracture. We also recruited healthy volunteers as the control group.

Patients with a neurological condition likely to confound the tests such as peripheral neuropathy, carpal tunnel syndrome, multiple sclerosis, stroke and Parkinson's disease were excluded from the study.

Patients were recruited from the outpatient Rheumatology clinics and healthy volunteers were recruited from the staff & medical students from the Cambridge University Hospitals NHS Foundation Trust.

Study Procedures

Baseline data were collected regarding date of diagnosis, age, sex, past medical history, current medications, body part affected (if CRPS or fracture) and hand dominance.

All patients completed five questionnaires assessing pain severity, physical function, depersonalisation and emotional state: Brief Pain Inventory (20), Upper Extremity Functional Index (21), Lower Extremity Functional Index (22), Neglect-like Symptom Questionnaire (8), Hospital Anxiety and Depression Score (23).

All patients and healthy controls completed four tests in the following order: Finger perception, hand laterality identification, astereognosis and body scheme report as described below.

Finger perception

FP was assessed bilaterally to allow intra-individual comparison between affected and unaffected sides. Ten touches were applied in a predefined order to the fingers of each hand, allowing clear standardisation between observers. No contiguous finger was consecutively touched. Time was measured as the total time from when the first finger was touched to when the last answer was given after the 10^{th} touch.

Regardless of the answer being correct or wrong for each touch, the next touch is applied as soon as the patient gives an answer. This continues till the 10 touches in total are applied per hand. If no answer was given, the test was finished after 60 seconds with the number of correct and incorrect answers recorded to give a percentage. Two outcome measures were generated: accuracy (%) and time (seconds). The test was administered in a stereotyped fashion and all the participants were given the following instruction:

"I'd like to test the sensation in your fingers with your eyes shut. I'd like to call your thumb number 1, index finger number 2 and so on to the little finger and similarly on your other hand. Please place your hands on your lap. Do not move your fingers when I touch them, but simply tell me the number corresponding to the finger that I touch. I will first touch your [left / right] hand and then move on to the other. Do you have any questions to me? Thank you. Please close your eyes and we will start."

Hand Laterality task

An in-house computer program presented 56 pre-loaded images in a random order. The patients and healthy controls identified each image as a left or right hand by clicking the mouse and this would generate the next image. The process continues till all 56 images have been presented. Two outcomes, accuracy (%) and time (seconds) were generated. The program calculates the accuracy out of a total possible score of 56. The 'time' taken was measured (using a stop watch) as the total time in seconds from the first image shown to the last response clicked.

Stereotyped instruction was given as follows: *"I would like to understand how quickly and reliably you can identify left and right hands presented to you using the*

computer programme. Please do not move your hand into the position shown but try to use mental imagery to decide whether the picture is of a left or right hand. Please select left or right using the mouse. We will time you and score how many you get right. Do you have any questions to me? Thank you."

Astereognosis

Patients and healthy controls were asked to feel an object with their eyes closed and identify it by touch using only one hand. Three common objects were used for each hand. A penny, paperclip and key were used for the right hand. Ten pence coin, bull dog clip and Micropore tape were used for the left hand. Two outcomes were measured for each hand: accuracy (%) and time (seconds).

Stereotyped instruction was given as follows: *"I would like to test whether you are able to identify different objects by touch only. I would like you to close your eyes and hold out your hand. I will put an object into the palm of your hand and I would like you to tell me what it is. You may move it around in your hand, but please don't transfer it to the other hand. I will first test your left/right hand and then test the other side. Do you have any questions? Thank you."*

Body scheme report

Patients and healthy controls compared the sensations from left and right sides of their body while deprived of visual (eyes closed) and motor feedback (instructed not to move).

21 areas were included : forehead; cheeks; chin; shoulders; upper arms; elbows; forearms; wrists; each digit; lower back; hips; thighs; knees; shins; ankles; big toes;

other toes. If an asymmetry was perceived, patients and healthy volunteers quantified the differences in size, length and heaviness, expressed as a percentage compared to the normal side.

Stereotyped instruction was given as follows: *"I would like to understand how you perceive your body with your eyes closed. I am going to ask you to close your eyes, keep your arms and legs still and describe how different parts of your body feel. I would like you to compare both sides in terms of size, weight and length as well as any other feelings you may be getting from those areas. I do not want you to move anything. We will start from your face and move down to your arms and legs. Do you have any questions to me? Thank you. Please close your eyes and we will start."*

Study Aims

The primary aim of the study was to measure the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio for the novel signs in the CRPS group compared to the Fracture group. The secondary aim of the study was to measure the prevalence of novel signs in different groups.

Statistical Analysis

Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio were calculated using MedCalc for Windows, version 12.7 (MedCalc Software, Ostend, Belgium). Kappa statistics, ROC curve analysis and ANOVA were performed using IBM SPSS Statistics for Windows, Version 20.0.

Defining a positive test for a novel sign

Data in 60 healthy volunteers and 49 CRPS patients was taken to determine the optimum 'cut off' for all tests. The sensitivity was plotted against the 1-specificity using every possible cut-off point of accuracy and time for finger perception and Hand Laterality and Receiver Operating Characteristic (ROC) curve analysis was performed (Figures 1 and 2).

The optimum sensitivity and specificity for FP was determined to correspond to an accuracy of <10/10 OR a time of >20 seconds. For HL the cut off was determined to be an accuracy of <50/56 AND a time of >100 seconds. AS was considered positive if the accuracy was <3/3 OR the time was >30 seconds. BS was summarized as a composite score, where an abnormal perception of two contiguous areas ≥5% (e.g. shoulder and upper arm or ankle and lower leg) was regarded as a positive test result.

Inter- and Intra-rater variability testing

Each investigator attended two 30-minute training sessions and was assessed that they were performing the clinical tests to the same standard. Five patients were tested for novel signs by four assessors separately during one session. The results showed that there was a high inter-rater agreement (Fleiss' Kappa=0.84, 95% CI= 0.6-1.0).

Nine recruits were tested on the novel signs on two separate occasions by the same investigator less than 4 weeks apart. There was a good strength of agreement between the results from 2 sessions (Cohen's Kappa=0.65, 95% CI= 0.02-1.0). There was therefore good reliability between and within assessors.

Ethical approval

The study was approved by the Research Ethics Committee, East of England (09/H0302/83). The study was adopted into the UK NIHR CRN portfolio (National Institute of Health Research, Clinical Research Network) (11545).

Results

Study Population

253 patients and 60 healthy (total of 313) were recruited into the study from a single centre between August 2009 and August 2013. The patients were recruited from the five different groups of CRPS (n=49), FMS (n=50), RA (n=60), LBP (n=47) and fracture (n=47). In the CRPS group, 31 (63%) had an upper limb affected and 18 (37%) had a lower limb affected. In the fracture group, 39 (83%) had upper limb fracture and eight (17%) had lower limb fracture.

The baseline characteristics of the patients and healthy controls are documented in Table 1. There was no significant age difference between the healthy volunteer and CRPS patients. The age of healthy controls was significantly lower than RA ($p < 0.001$), FMS ($p < 0.002$), LBP ($p < 0.001$) and Fracture patients ($p < 0.001$). The proportion of females in the study ranged from 55.3% in the fracture group to 92% in the FMS group. The majority in each group (ranging from 78.7% in the LBP group to 89.3% in the fracture group) were right handed.

Questionnaires Results

The data on pain severity, physical function, emotional state and depersonalisation are summarised in Table 2.

The patients in the CRPS group had the highest pain, anxiety and depression scores and the lowest functional scores although these differences were not statistically significant. There was a significant difference between the mean NLSQ scores of different groups (p<0.001) being significantly higher in the CRPS group compared to all other groups.

None of the scores from the questionnaire data correlated significantly with any of the novel signs in any group.

Clinical Outcomes

The prevalence of the four novel signs is shown in Table 3.
35% of the healthy volunteer did not have a single positive sign compared to at least one positive test in all 49 patients with chronic CRPS. Furthermore 9/16 patients with four positive tests had a diagnosis of CRPS. 67.3% of the CRPS group had 3 or more signs, compared with 3.3% of the healthy volunteer group and 13.3%; 21.3%; 27.7%; 32% in the RA; LBP; Fracture and FMS groups respectively. Of interest is that there was no significant difference in the prevalence of positive clinical signs in the CRPS group when comparing upper and lower limb involvement in either the CRPS group (p=0.15) or the fracture group (p=0.38).

Table 4 demonstrates the prevalence of each of the signs across all of the groups. BS had a very high prevalence in the CRPS group (93.9%) that was significant ($p<0.001$) when compared to all of the other groups (23-50%). FP was also significantly higher ($p<0.01$) in the CRPS group (85.6%) when compared to the other groups (23-62%). HL was very prevalent in all chronic pain groups – CRPS (69.4%), FMS (72%), RA (76.7%) and LBP (63.8%). AS had the lowest prevalence within each group (12-36%) with no significant differences between the groups.

Clinical utility data for each of the signs are summarised in Table 5 comparing the CRPS group to the fracture group. BS had the highest sensitivity (93.9%) and specificity (72.3%). The absence of BS was clinically useful in being able to rule out CRPS (91.9% negative predictive value with a negative LR of 0.1). Combining the two best performing tests of FP & BS improves the specificity (85.1%) with a high positive predictive value (84.1%).

Fracture follow-up

We reviewed the electronic hospital records of all 47 fracture patients in the study to assess the clinical progress for a mean duration of 3.2 years (range 1.5-5). 4/47 (8.5%) patients had persistent pain as documented by the clinical record. Out of 7 patients who were positive for both FP and BS report at initial testing, 3 had persistent pain with one having a formal diagnosis of CRPS. Another patient (who was negative for both finger perception and body scheme report) also had persistent pain but this was attributed to the severity of injury (i.e. not disproportionate pain) and there were no clinical signs of CRPS. There was no significant correlation between baseline pain report and the development of chronic pain.

Discussion

Previous studies have reported the presence of novel signs in CRPS (8,9,11,12). However, the clinical diagnostic utility of these signs in CRPS have not been established previously in a systematic fashion.

We recruited a large cohort of patients (253 patients in five different groups of CRPS, FMS, RA, LBP and Fracture) and healthy controls (60 healthy) and objectively defined bedside tests for FP, HL, BS and AS. We validated these tests with a small number of assessors following a short training programme and the results showed that there was good intra- and inter-rater agreement. An ROC curve analysis was carried out to determine the cut-offs for optimum sensitivity and specificity. These were then used to calculate the prevalence of the novel signs in different groups.

Förderreuther et al had reported that 48 % had impaired accuracy to identify fingers in the affected hand compared to contra-lateral hand in their study of 73 CRPS patients(9). However, this study did not take into account the time delay (latency) in responding to the touch. We used both accuracy and time (latency) to define the cut-offs and we found that a higher proportion (85.6% of 49 patients) had finger misperception.

Reinersmann et al reported delayed reaction time and reduced accuracy in limb laterality recognition in CRPS and Phantom limb pain patients compared to healthy controls(11). However, this was a small study (n=12) and also did not assess the presence of this sign in other chronic pain conditions unlike our study. Our findings

demonstrate that these signs are not unique to patients with CRPS, but appear in all chronic pain groups.

There was no relationship between the presence of a positive test and self-reported pain scores; anxiety and depression scores; nor functional scores. The study was not powered to detect such differences however and further work is needed to explore any possible relationships.

We calculated the diagnostic clinical utility (sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio) of novel signs in patients with CRPS. BS had the highest positive predictive value (78%) and the highest negative predictive value (91.9%). The diagnostic clinical utility was further increased by combining the two best performing tests of FP and BS as a composite test.

There are many predictors of chronic pain following trauma. These include leaving education early; low self-efficacy scores; high baseline pain scores; high levels of sleep disturbance; and high levels of depression and anxiety (24). None of these predictors perform well enough to predict persistent pain in the acute phase. Moseley et al report that a pain score of less than 5 rules out a diagnosis of CRPS (2). 10/47 patients recorded a baseline pain VAS of 5+ in our cohort and yet only 4 developed persistent pain of which 2/4 patients had a baseline average pain score of <5/10. We were therefore unable to replicate Moseley's findings in our smaller cohort and it seems unlikely that using pain scores *per se* will be a sufficient marker to predict persistent post-fracture pain. It's possible that this difference reflects the

timing of when the question was asked with Moseley's cohort being asked within the first week, whereas patients in this cohort were captured within 4 weeks of the injury.

Tests of altered body scheme are much more predictive. The absence of either abnormal finger perception or body scheme report was highly predictive of the absence of persistent pain. Their presence was associated with a significant increase in the presence of persistent pain. These findings support Moseley et al's findings that dysynchiria (bilateral sensations when one limb is touched) is a strong predictor of CRPS when present. Assessing for dysynchiria takes 25 minutes and would not be practical in a clinical setting. Finger perception and abnormal body scheme assessments take less than 5 minutes to perform. Using these tests will stratify patients rapidly into those 'at risk' of developing persistent pain including CRPS; and those who are not. The prevalence of both signs together is 14.9% thus stratifying a manageable cohort in the Fracture clinic for targeted intervention, such as education, physiotherapy and analgesics.

This is a single centre study and the numbers included are small. In this study the optimum cut-offs for each test were derived and then the prevalences of positive signs estimated using the same dataset. Validation of the optimum cut-offs is required in future studies using independent data. The healthy volunteer group were importantly balanced in terms of age to the CRPS group, but were younger than the patient groups of LBP, FMS, RA and Fracture. This significant age difference is likely to under-estimate the predictive values. Patients with CRPS were more likely to be taking anti-neuropathic agents or anti-depressants. Both of these groups of drugs have cognitive side effects. It's doubtful that these medications contribute

significantly to the presence of signs as the RA and Fracture demonstrated a high prevalence of signs but very few patients took these medications.

These bedside tests assess higher cognitive functions, known to be disrupted in some patients with CRPS and correlating to the size of mechanical allodynia (13). FP did not correlate with the site of chronic pain suggesting that abnormal central processing is the dominant mechanism. Serial functional neuroimaging studies in these patient groups may provide further evidence and possible therapeutic targets in this regard. The pain phenotype may be better understood if future studies take into account changes in the body scheme.

Conclusions

Novel signs of FP, HL, BS, AS are present in CRPS patients and have significant clinical diagnostic utility. They are also present in other chronically painful conditions such as rheumatoid arthritis, fibromyalgia syndrome and low back pain. Combining FP and BS is helpful in stratifying a cohort of at risk patients post-fracture. It is a quick, simple and reliable test that can easily be taught. The pain phenotype may be better understood by assessing for changes in body scheme.

Article Information

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Author Contributions: Dr Nicholas Shenker had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Shaikh, Shenker

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Drafting of the manuscript: Kuttikat, Shenker

Critical revision of the manuscript for important intellectual content: Kuttikat, Shaikh, Shenker

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Study supervision: Shenker

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Figure Legends

Figure 1: Receiver Operating Characteristic (ROC) plot with data points representing the sensitivity and 1-specificity corresponding to every possible cut-off point combination of thresholds of time and accuracy for the finger perception test. This was constructed based on using the affected arm of CRPS patients and the non-dominant hand of healthy patients. The optimum cut-off point combination is when Accuracy<10 or Time> 20 seconds indicates a positive test, corresponding to a sensitivity of 88% and specificity of 88%.

Figure 2: Receiver Operating Characteristic (ROC) plot with data points representing the sensitivity and 1-specificity corresponding to every possible cut-off point combination of thresholds of time and accuracy when using the Hand laterality test to diagnose CRPS. The optimum cut-off point combination is when Accuracy<50 and time>100 seconds indicates a positive test for CRPS, corresponding to a sensitivity of 69% and specificity of 70%.

Figure 1

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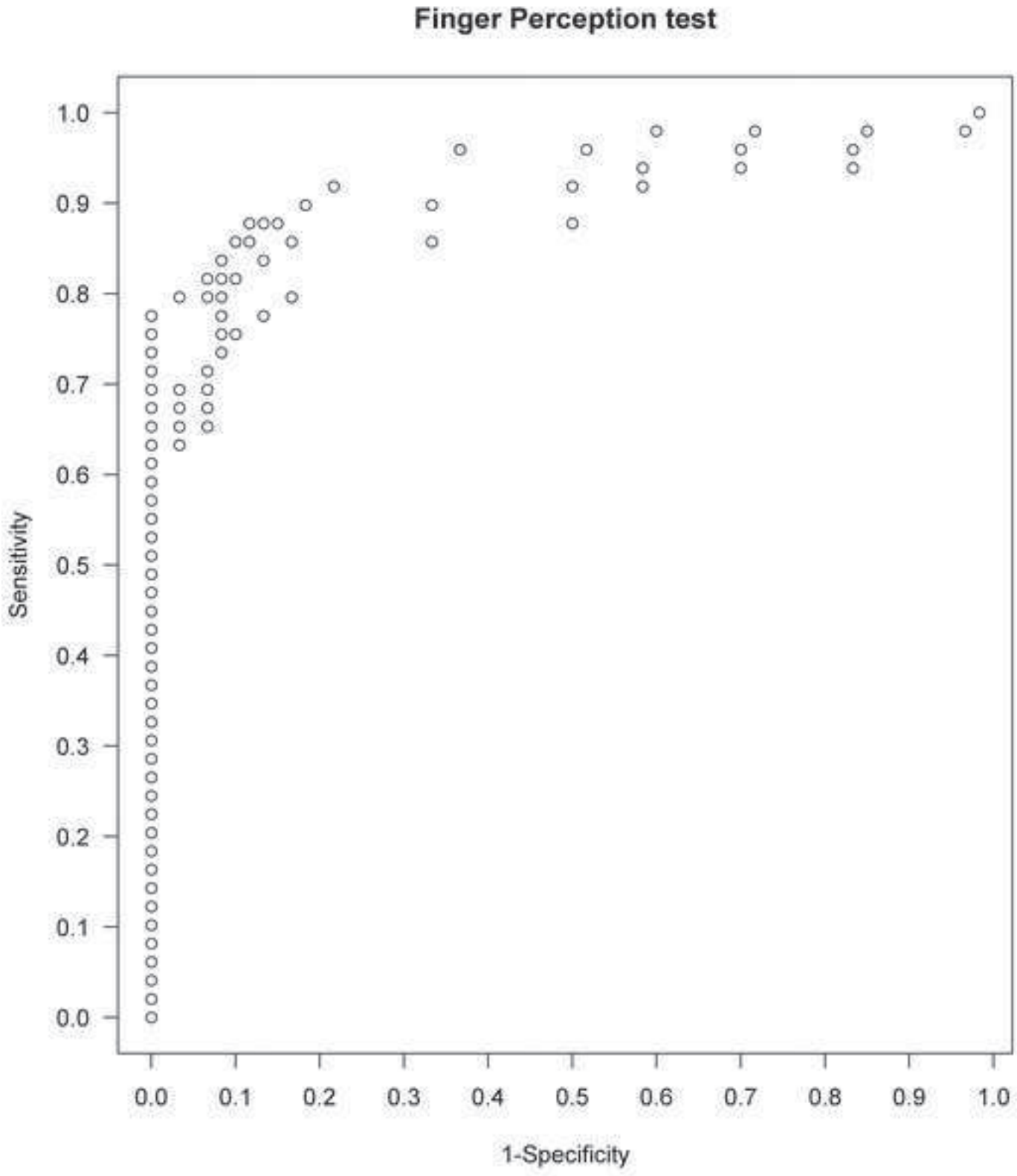

Figure 2

Click here to download Figure Fig 2-HandLaterality.ROC.New.tiff

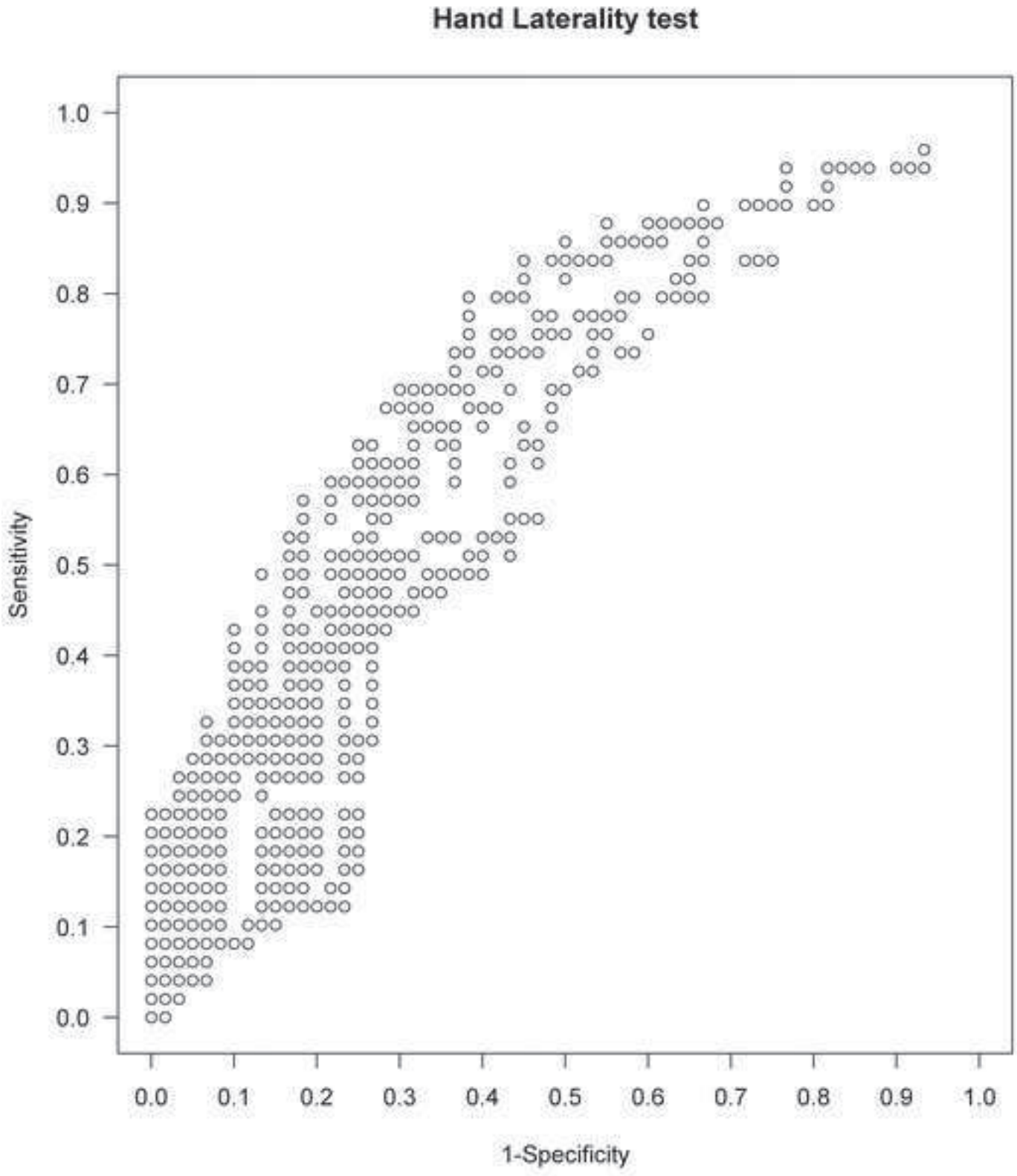

Table 1: Baseline characteristics of subjects

Characteristics	HV (n=60)	CRPS (n=49)	FMS (n-50)	RA (n=60)	LBP (n=47)	Fracture (n=47)
Age in years Mean (range)	36.1 (20-64)	43.6 (18-64)	46.7 (22–80)	55.4 (22-78)	54.0 (20-85)	53.6 (19-88)
Female sex (%)	47 (78.3)	39 (79.6)	46 (92)	47 (78.3)	33 (70.2)	26 (55.3)
Right handed (%)	52 (86.6)	42 (85.7)	41 (82)	50 (83.3)	37 (78.7)	42 (89.3)
Disease duration in years Mean (range)	N/A	3.5 (0.5-10)	4.0 (0.5-22)	11.6 (1-50)	10 (1-40)	N/A
Past medical history						
Depression/Anxiety	**none**	**39 (79.6)**	**28 (56.0)**	**14 (23.3)**	**16 (34.0)**	**3 (6.4)**
Other psychiatric		0	2 (4.0)	1(1.7)	0	0
IBS		**2 (4.0)**	**1 (2.0)**	**0**	**2 (4.2)**	**0**
Asthma/COPD		8 (16.3)	10 (20.0)	7 (11.7)	2 (4.2)	2 (4.2)
Migraines		**1 (2.0)**	**2 (4.0)**	**0**	**0**	**0**
Other medical		24 (48.9)	23 (46.0)	25 (41.7)	21 (44.7)	15 (31.9)
Medications at the time of study (%)						
Paracetamol	**none**	**16 (32.6)**	**12 (24.0)**	**14 (23.3)**	**18 (38.3)**	**8 (17.0)**
NSAIDs		6 (12.2)	5 (10.0)	12 (20.0)	8(17.0)	1 (2.1)
Weak opioids		**22 (45)**	**11(22.0)**	**7(11.6)**	**11(23.4)**	**4(8.5)**
Strong opioids		10(20.4)	5 (10.0)	2(3.3)	2(4.2)	1(2.1)
Anti-depressants		**22 (45)**	**13 (26.0)**	**3(5.0)**	**7(14.9)**	**0**
Anti-convulsants		28(57.1)	14(28.0)	0	7(14.9)	0
Other medications		**8(16.3)**	**10(20.0)**	**59(98.3)**	**11(23.4)**	**8(17.0)**

N/A - Not applicable

Patients in the fracture group were recruited within 2 weeks of the fracture

Table 2: Summary of questionnaires data

Category	CRPS (n=49)	FMS (n-50)	RA (n=60)	LBP (n=47)	Fracture (n=47)
Maximum Pain (0-10), 10 worst	8.00 (1.68)	7.34 (1.25)	4.81 (2.6)	6.53 (2.02)	3.31 (2.61)
Least Pain (0-10)	5.74 (2.29)	4.50 (2.62)	2.41 (1.91)	3.63 (2.42)	1.44 (2.03)
Average Pain (0-10)	6.59 (1.86)	5.80 (1.78)	3.85 (1.92)	5.29 (1.66)	2.41 (2.18)
Current Pain (0-10)	7.38 (1.45)	7.20 (1.30)	4.53 (2.30)	6.42 (1.93)	2.31 (1.98)
Pain Interference (Average) (0-10)	7.06 (2.14)	6.43 (1.88)	3.97 (2.47)	5.23 (2.42)	2.54 (2.24)
UEFI (0-80), 80 best	34.80 (25.58)	35.60 (16.48)	50.46 (19.82)	48.17 (21.28)	36.72 (22.51)
LEFI (0-80), 80 best	29.20 (21.39)	34.36 (18.34)	43.78 (22.52)	33.25 (21.64)	63.65 (25.37)
HAD-Anxiety (0-21), 21 worst	11.10 (4.31)	11.00 (4.64)	6.70 (4.02)	7.68 (4.71)	3.89 (2.69)
HAD-Depression (0-21), 21 worst	10.71 (3.91)	9.44 (4.66)	5.15 (3.55)	7.51 (5.11)	3.93 (3.17)
NLSQ-Average (1-6), 6 worst	4.21 (0.95)	2.88 (1.29)	2.36 (1.26)	2.32 (1.24)	2.17 (1.19)

Mean scores for each group with standard deviations in brackets.

UEFI/LEFI Upper/Lower Extremity Functional Index; HAD Hospital Anxiety and Depression; NLSQ Neglect Like Symptom Questionnaire

Table 3: Numbers of clinical signs in each group

Category	0 sign	1 sign	2 signs	3 signs	4 signs	≥1 sign	≥2 signs	≥3 signs
HV (n=60)	21 (35%)	26 (43.3%)	11 (18.3%)	1 (1.6%)	1 (1.6%)	39 (65%)	14 (23.3%)	2 (3.3%)
CRPS (n=49)	0	3 (6.1%)	13 (26.5%)	24 (48.9%)	9 (18.4%)	49 (100%)	46 (93.8%)	33 (67.3%)
FMS (n-50)	0 (0%)	12 (24%)	22 (44%)	13 (26%)	3 (6%)	50 (100%)	38 (76%)	16 (32%)
RA (n=60)	3 (5%)	20 (33.3%)	29 (48.3%)	7 (11.7%)	1 (1.7%)	57 (95%)	37 (61.7%)	8 (13.3%)
LBP (n=47)	6 (12.7%)	14 (29.7%)	17 (36.2%)	9 (19.1%)	1 (2.1%)	41 (87.2%)	27 (57.4%)	10 (21.3%)
Fracture (n=47)	6 (12.8%)	15 (31.9%)	13 (27.6%)	12 (25.5%)	1 (2.1%)	41 (87.2%)	26 (55.3%)	13 (27.7%)
Fracture 6 months (n=20)	2 (10%)	6 (30%)	10 (50%)	2 (10%)	0	18 (90%)	12 (60%)	2 (10%)

(Table 3 shows number (percentage in brackets) of recruits in each group with the following number of positive clinical signs: No sign, 1 sign, 2 signs, 3 signs, 4 signs, ≥1 sign, ≥2 signs & ≥3 signs)

Table 4: Prevalence of novel signs in all groups

Category	Finger Perception +	Hand Laterality +	Astereo-gnosis +	Body scheme +	FP+ AND BS+
HV (n=60)	14 (23.3%)	18 (30.0%)	7 (11.6%)	14 (23.3%)	6 (10.0%)
CRPS (n=49)	42 (85.6%)	34 (69.4%)	14 (28.6%)	46 (93.9%)	37 (75.5%)
FMS (n-50)	28 (56.0%)	36 (72.0%)	18 (36.0%)	25 (50.0%)	11 (22.0%)
RA (n=60)	33 (55.0%)	46 (76.7%)	14 (23.3%)	17 (28.3%)	6 (10.0%)
LBP (n=47)	24 (51.1%)	30 (63.8%)	13 (27.6%)	20 (42.6%)	11 (23.4%)
Fracture (n=47)	29 (61.7%)	26 (55.3%)	14 (29.8%)	13 (27.7%)	7 (14.9%)
Fracture (6 months) (n=20)	13 (65.0%)	12 (60.0%)	2 (10.0%)	4 (20.0%)	1 (5.0%)

Table 4 shows the prevalence of the clinical signs (Finger Perception, Hand Laterality, Astereognosis, Body scheme & composite of the two best performing signs (Finger Perception & Body Scheme report) in the different groups. Percentages are given in brackets.

Table 5: Clinical utility of novel clinical signs in CRPS (n=49) compared to Fracture group (n=47)

	Sn	Sp	PPV	NPV	PLR	NLR
Finger Perception+	85.7% (72.7- 94.0)	38.3% (24.5-53.6)	59.1% (46.8-70.6)	72.0% (50.6-87.9)	1.4 (1.1-1.8)	0.4 (0.2-0.8)
Hand Laterality +	69.3% (54.5-81.7)	44.6% (30.1-59.8)	56.6% (43.2-69.4)	58.3% (40.7-74.4)	1.2 (0.9-1.7)	0.7 (0.4-1.2)
Astereo-Gnosis +	28.5% (16.6-43.2)	70.2% (55.1-82.6)	50.0% (30.7-69.3)	48.5% (36.2-61.0)	1.0 (0.5-1.8)	1.0 (0.8-1.3)
Body Scheme +	93.9% (83.1-98.6)	72.3% (57.4-84.4)	78.0% (65.3-87.7)	91.9% (78.1-98.2)	3.4 (2.1-5.4)	0.1 (0.0-0.3)
FP+ AND BS+	75.5% (61.1-86.6)	85.1% (71.7-93.8)	84.1% (69.9-93.3)	76.9% (63.2-87.4)	5.1 (2.5-10.2)	0.3 (0.2-0.5)
≥1 sign +	100% (92.7-100)	12.7% (4.8-25.7)	54.4% (43.6-64.9)	100% (54.1-100)	1.2 (1.0-1.3)	0
All 4 signs +	18.3% (8.7-32.0)	97.8% (88.7-99.9)	90.0% (55.5- 99.7)	53.5% (42.4-64.3)	8.6 (1.1- 65.5)	0.8 (0.7-1.0)

(Sn=Sensitivity, Sp=Specificity, PPV=Positive Predictive Value, NPV=Negative Predictive Value, PLR=Positive Likelihood Ratio, NLR=Negative Likelihood Ratio)

*95% confidence intervals in brackets